Pestic. Sci. 1998, **52**, 21–28

Synthetic Pyrethroids Containing a C–C Triple Bond*

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(Received 15 July 1997; accepted 24 September 1997)

Abstract: The three commercial synthetic pyrethroids containing a carbon–carbon triple bond, α-ethynyl-2-methylpent-2-enyl (1*R*)-*trans*-chrysanthemate, (*S*)-2-methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl (1*R*)-*trans,cis*-chrysanthemate and [2,5-dioxo-3-(2-propynyl)-1-imidazolidinyl]methyl (1*R*)-*trans*-chrysanthemate are reviewed with emphasis on their inventive histories. Their chemistry and efficacy are described briefly. The relationship between stereochemistry and the biological activity is also discussed. © 1998 SCI.

Pestic. Sci., **52**, 21–28, 1998

Key words: synthetic pyrethroids; structure–activity relationship; carbon–carbon triple bond; insecticidal activity; knockdown activity; stereochemistry; conformation analysis

1 INTRODUCTION

The study of structural modification of natural pyrethrins has lasted for more than half a century. Especially, the discovery of allethrin, 2-methyl-4-oxo-3-allylcyclopent-2-enyl chrysanthemate, prompted chemists to make structural modifications of the pyrethroid alcohol and acid moieties. As a result, a number of synthetic pyrethroids with diversified characteristics have been invented not only for the control of household insect pests but also for agricultural use.

Further exploratory work in our laboratory on modification of the alcohol moieties of natural pyrethrins resulted in a series of discoveries of important pyrethroids containing a carbon–carbon triple bond, of which empenthrin, α-ethynyl-2-methylpent-2-enyl (1*R*)-*trans*-chrysanthemate, was noteworthy for its high volatility which enabled control of cloth insect pests in closets.

Second, we showed that the propynyl analogue of allethrin had more than twice the knockdown and lethal activity of allethrin against mosquitoes and houseflies. The most active stereoisomer of this compound has been commercialised.

Another important compound containing a carbon–carbon triple bond discovered in this laboratory was a propynyl hydantoinmethyl alcohol, the ester of which with (1*R*)-*trans*-chrysanthemic acid is one of the most powerful knockdown agents. Here superimposition of imiprothrin with two other pyrethroid esters is studied using the most active stereoisomers and considering the fitting of both steric and electrostatic fields.

2 MATERIALS AND METHODS

2.1 Test species

Stock colonies of the following species were reared in this laboratory at 27(±1)°C and 60(±5)% relative humidity: Housefly *Musca domestica* L., CSMA or WHO strain (susceptible); Cockroach *Blattella germanica* L., Sumitomo strain (susceptible); Mosquito

* Presented at the International Award for Research in Agrochemicals Symposium in Honour of Klaus Naumann at 212th ACS National Meeting in Orlando, FL, USA 25–29 August 1996.

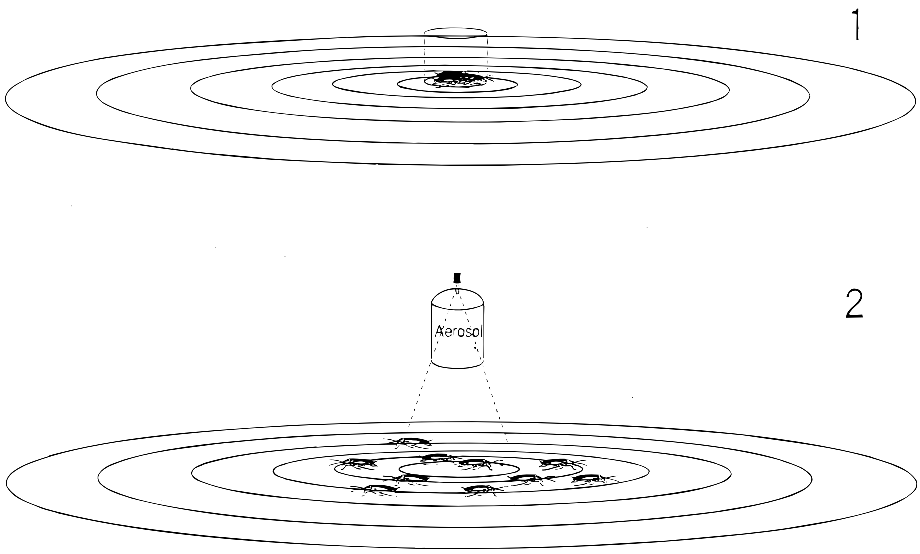

Fig. 1. Evaluation method by distance of cockroaches' movement after treatment.

Culex pipiens pallens Coquillett, Gose strain (susceptible).

2.2 Methods

2.2.1 *A new test for knockdown activity*

A new method for evaluation of knockdown activity against cockroaches, designed by Senbo *et al.*[1] and illustrated in Fig. 1, was termed the 'darts method'. Ten German cockroaches (five male and five female) were confined in a plastic ring placed at the centre of a series of concentric circles (10 cm apart) inscribed on a poly(vinyl chloride) sheet. They were sprayed with the test compound (1 g in an oil-based aerosol formulation) from a height of 60 cm, the plastic ring was removed immediately and the cockroaches allowed to run away. The distance from the centre achieved by each insect was measured and recorded; any cockroach over-running the sheet was considered to have moved >140 cm. The MD_{50} (the mean distance moved) for each test formulation was calculated according to Finney's method.

2.2.2 *Calculation method for conformation analyses*

A conformation analysis was carried out according to the AM1 semi-empirical molecular orbital method in the MOPAC 93 program.[2] Initial geometry of each molecule for the conformational analysis was generated by the systematic search method in the SYBYL molecular modeling program. Bonds defined were rotated. (See Fig. 12). The torsion increment was set to 60 degrees. All scaling factors to eliminate sterically hindered conformations were set to 0·6. Superposition of each of the molecules, (*S*)-**16**, (*R*)-**16**, **22** and (*R*)-**22** on the most stable conformer of imiprothrin **26** was carried out by the field fit method in the SYBYL programme. Since geometries of the molecule fitted with the field fit method were distorted, these were optimised by the AM1 method. During optimisation, torsion angles 1-2-3-4, 3-4-5-6, 5-6-7-8 and 8-9-10-11 were fixed for **22** and (*R*)-**22** and torsion angles 1-2-3-4, 3-4-5-6, 5-6-7-8, 6-7-8-9 and 8-9-10-11 were fixed for (*S*)-**16** and (*R*)-**16** in order to retain fitted conformations. Conformational energies (difference in energy level between the fitted conformer and the most stable one) were calculated for these geometries by the AM1 method.

3 RESULTS AND DISCUSSION

3.1 A volatile synthetic pyrethroid, empenthrin

3.1.1 *Background*

Fission of the cyclopentenolone ring of allethrolone **2**, an alcohol moiety of allethrin **1**, or 2-methyl-4-oxo-3-allylcyclopent-2-enone was first tried by Sota,[3] which resulted in finding an important acyclic alcohol ester **3** (Fig. 2). Although this ester was not commercialised, it became the prototype of our volatile pyrethroid.

It often happens that an impurity can give us a rare opportunity for a new invention. In fact, during process research with 5-(2-propynyl)-2-furfuryl alcohol **5** whose ester **4** with chrysanthemic acid was synthesised by Katsuda[4] and, on coils, had good knockdown and killing activity against mosquitoes, α-ethynyl-5-(2-propynyl)-2-furfuryl alcohol (**9**) was obtained unex-

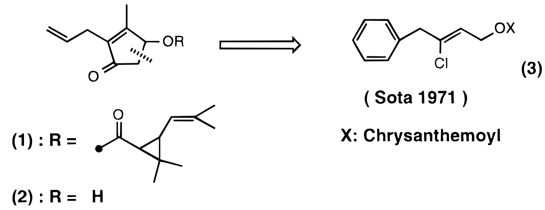

Fig. 2. Development of acyclic alcohol moiety.

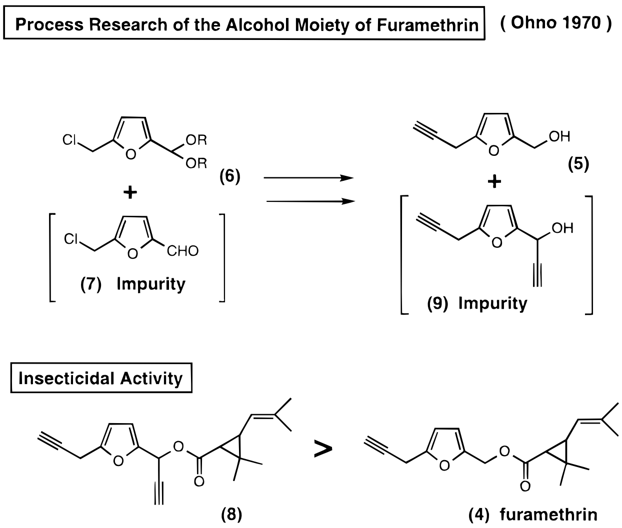

Fig. 3. Background of empenthrin-1.

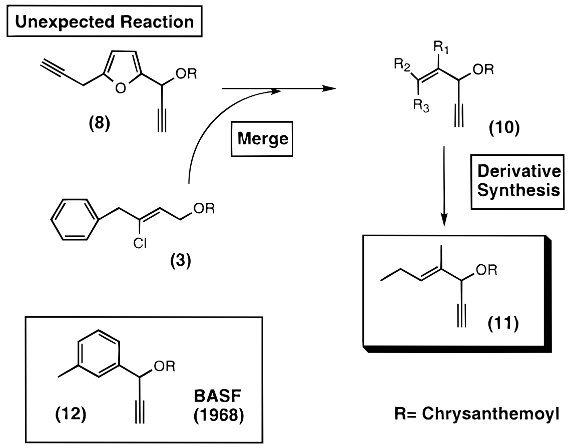

Fig. 4. Background of empenthrin-2 (Kitamura 1973).

pectedly by Ohno due to contamination of the starting acetal **6** with a small amount of 5-chloromethyl-2-furfural **7** (Ohno, N., unpublished; Fig. 3). To our surprise, the chrysanthemate **8** of this α-ethynyl alcohol had almost twice the efficacy of furamethrin (**4**). Although the ester **8** was not commercialised because of its instability, this finding prompted us to synthesise derivatives, taking advantage of our unexpected finding of the reaction of α-ethynyl carbinols with the acyclic alcohol **3**. Merging of these two concepts resulted in new acyclic α-ethynyl carbinol esters, **10**. Further derivative syntheses by Kitamura[5] finally yielded empenthrin **11** (Fig. 4). α-Ethynylbenzyl esters (**12**) were already reported as synthetic pyrethroids in 1968.[6] However, the present invention stemmed not from the literature but from merging of the two ideas mentioned above.

3.1.2 Vapour pressure and activity

Figure 5 shows the relationship of molecular weight and vapour pressure of various pyrethroids. The abscissa shows the molecular weight. The vertical line shows the vapour pressure at room temperature. It is apparent that the vapour pressure of empenthrin is the highest, and proved to be sufficient for the compound to be used as a fumigant in confined spaces to control insect pests attacking fabrics.

The activity of empenthrin (**11**) against *M. domestica* compares well with that of optically active *d*-allethrin when applied topically, as shown in Table 1, and it is notable that its knockdown activity and lethal activity at room temperature are much greater. This is due to the fact that the vapour pressure of empenthrin at 25°C is 15 times greater than that of *d*-allethrin.

3.1.3 Synthesis of the optically active alcohol moiety of empenthrin

The optically active alcohol moiety of empenthrin was obtained by microbial resolution of the racemic acetate using *Bacillus subtilis* (Eherenberg) Cohn *var niger* (Fig. 6). The intact *S*-acetate, together with the hydrolysed *R*-alcohol, was obtained in moderate enantio-excess. The absolute configuration of the hydrolysed alcohol was rigorously confirmed to be *R* by correlation to the known α-aminobutyric acid.

The relative lethal activity of empenthrin is compared with that of the optically active empenthrins in Table 2. (*S*)-Empenthrin, which is the ester of (*S*)-alcohol with (1*R*)-*trans*-chrysanthemic acid, has twice the activity of empenthrin, whereas (*R*)-empenthrin has substantially no activity considering the enantio-excess of the alcohol moiety.

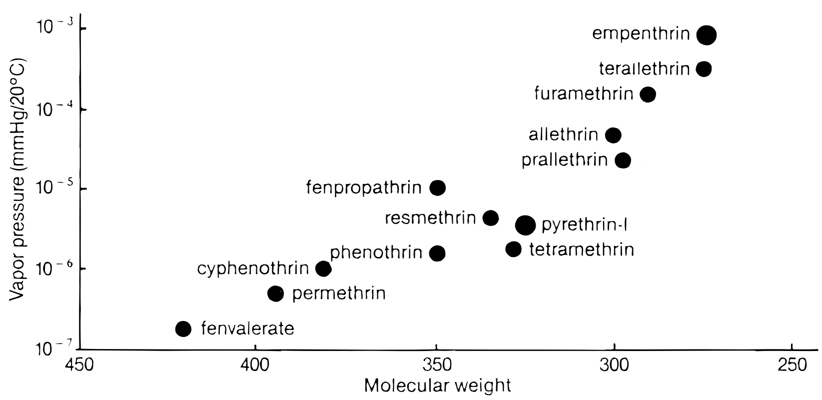

Fig. 5. Relationship between the molecular weights of pyrethroid compounds and their vapour pressures.

TABLE 1
Vapour Effect of Empenthrin against *Musca domestica*

	Topical application LD_{50} (*μg per female*)	*Vapour effect at 25°C* kT_{50} (*min*)[a]	*Vapour effect at 25°C* *Mortality* (%)	*Vapour pressure at 25°C* (*mm Hg*)
empenthrin (**11**)	0·25	14	100	$1{\cdot}1 \times 10^{-3}$
d-allethrin	0·25	>120	3	$7{\cdot}6 \times 10^{-5}$

[a] Knockdown activity.

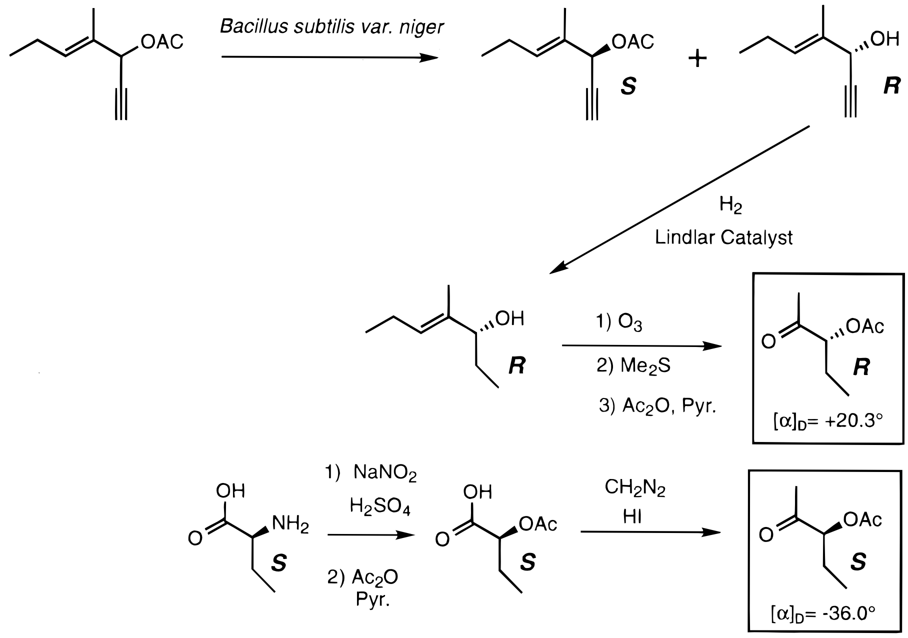

Fig. 6. Synthesis of optically active empenthrin alcohol (Matsuo 1980).

3.2 Prallethrin a synthetic pyrethroid for use in coils

3.2.1 Microbial resolution of α-ethynyl alcohols—a hint to further discovery

The optically active α-ethynyl acetates, (*S*)-**13**, (*R*)-**14**, (*S*)-**15** (Fig. 7) were prepared by enzymatic hydrolysis using the same bacterium mentioned above. Although (*R*)-**14** is geometrically equivalent to (*S*)-**13** and (*S*)-**15**, their (*R*) and (*S*) descriptors differ owing to the sequence rule. The absolute configurations were all confirmed by correlation with known compounds.[7,8] Independent of unsaturation on the side chain and substitution on the 2-position (**13**, **14**, **15**), this microbe gives the same absolute configuration, as shown in Fig. 7.

TABLE 2
Relative Insecticidal Activity of the Optical Isomers of α-Ethynyl-2-methylpent-2-enyl-(1*R*)-*trans*-chrysanthemate against *Musca domestica*

Optical isomers *Alcohol moiety*	*Optical isomers* *Acid moiety*	*Relative insecticidal activity* M. domestica
α*S*	(1*R*)-*trans*	240
α*SR*	(1*R*)-*trans* (empenthrin)	100
α*R*	(1*R*)-*trans*	35

During process studies of the microbial resolution of α-ethynyl alcohols, we noticed a greater than two-fold difference in activity between propynyl(**16**) and allyl(**17**) substituted compounds, as shown in Fig. 8. By analogy, it was presumed that the insecticidal activity of the

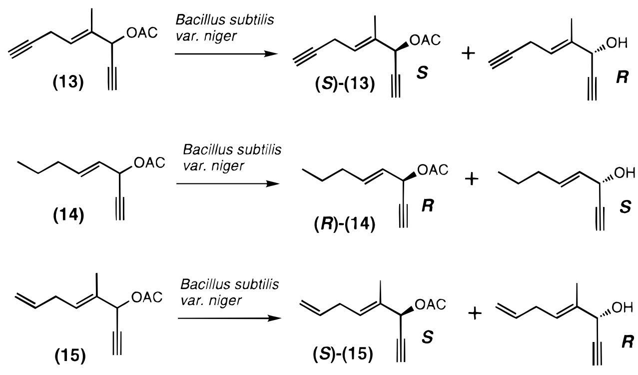

Fig. 7. Synthesis of optically active empenthrin alcohol derivatives (Matsuo 1981).

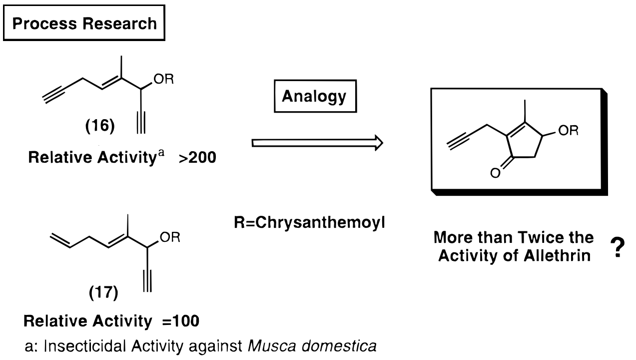

Fig. 8. Background of prallethrin.

propynyl analogue of allethrin might be more than twice that of allethrin (**1**) which has an allyl side chain.

3.2.2 *Efficacy of the propynyl analogue of allethrin*

The propynyl analogue, **18**, of allethrin was first synthesised by Gersdorff in 1961,[9] but it did not attract much attention at that time, since its efficacy was reported to be only 60% of that of allethrin (**1**) against houseflies. In 1974 Katsuda re-evaluated **18** and found it to be slightly more active than allethrin,[4] although the activity was not attractive enough to investigate the synthetic pathways of the alcohol moiety (**19**) for large-scale production. In fact, we found that the alcohol moiety **19** was easily transformed to the allene alcohol **21** in a basic medium (Fig. 9). Since the ester **20** showed low insecticidal activity, it was considered that the propargyl analogue of allethrin produced by Gersdorff might have been impure. We prepared pure **19**[10] and re-examined the insecticidal activity of the ester **18**, which was found to be more than twice as active as allethrin against various insect pests with regard to the knockdown and lethal activities.

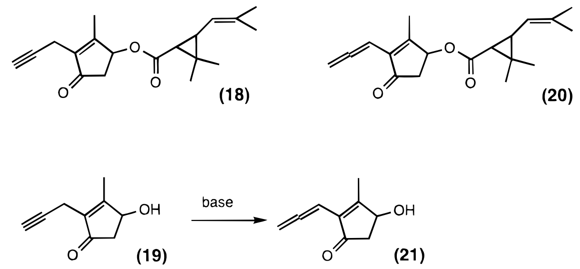

Fig. 9. A propynyl analogue of allethrin.

TABLE 3
Insecticidal Activity of Optical Isomers of Prallethrin against *Musca domestica*

Optical isomers		LD_{50}
Alcohol moiety	*Acid moiety*	(μg *per female*)
S	(1*R*)-*trans*	0·043
S	(1*R*)-*cis*	0·11
R	(1*R*)-*trans*	0·25
R	(1*R*)-*cis*	0·32
S	(1*S*)-*trans*	3·30
S	(1*S*)-*cis*	10·8
S	(1*S*)-*trans*	18·5
R	(1*S*)-*cis*	28·2
Natural pyrethrin		0·73

3.2.3 *Chemistry of prallethrin*

It is often found that biological activity resides in a specific stereoisomer of an enantiomer pair. This is the case with compound **18**. There are three asymmetric carbon atoms in this compound, and thus eight stereoisomers exist. Table 3 shows the insecticidal activity of these eight stereoisomers against *M. domestica.* Chrysanthemic acid possesses two asymmetric centres and the (1*R*)-*trans* and (1*R*)-*cis* isomers provide insecticidal esters.

With regard to the alcohol moiety, only the (*S*)-isomer is insecticidally important. Thus among the eight isomers, the ester of the (*S*)-alcohol with (1*R*)-*trans*-chrysanthemic acid is the most active isomer. The ester of the (*S*)-alcohol with (1*R*)-*trans,cis*-chrysanthemic acid is commercialised as prallethrin, **22**. The relative lethal and knockdown activities of prallethrin in comparison with *d*-allethrin are shown in Table 4. Prallethrin is more than four times as active as *d*-allethrin against *M. domestica* and *B. germanica* in lethal activity, and has much better knockdown activity than *d*-allethrin against *Culex pipiens pallens.*

The synthesis of the alcohol moiety of prallethrin was conducted by Umemura[11] as shown in Fig. 10. The key steps of this synthesis involve the combination of enzymatic resolution of the racemic acetate **23** and chemical inversion of the hydrolysed alcohol (*R*)-**19**. Thus, the reaction mixture from the enzyme reaction was treated

TABLE 4
Relative Lethal and Knockdown Activity of Prallethrin in Comparison with *d*-Allethrin

	Relative lethal activity[a]		*Relative knockdown activity*[b]
Insecticide	M. domestica	B. germanica	C. pipiens
Prallethrin	420	610	470
d-Allethrin	100	100	100

[a] Topical application, LD_{50} μg per female.
[b] Oil spray, 0·34 m^3 glass chamber.

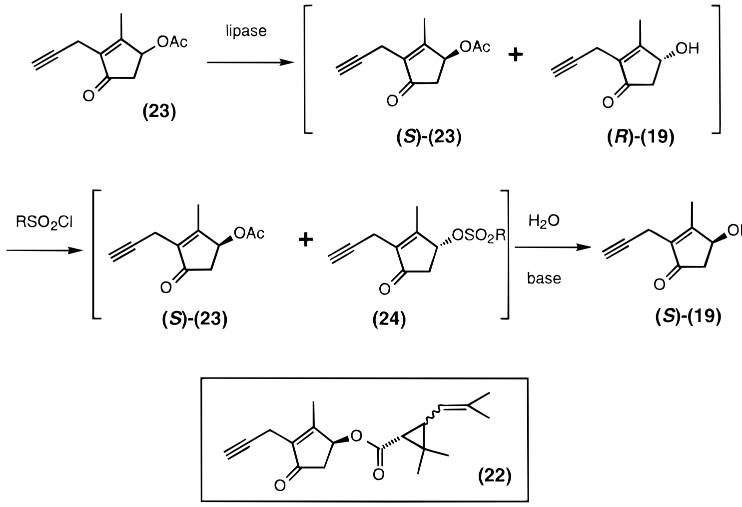

Fig. 10. Synthesis of the alcohol moiety of prallethrin (Umemura 1988).

with alkane sulphonylchloride to give a mixture of (*S*)-acetate, (*S*)-**23** and the (*R*)-sulfonate **24**. The two different esters were found to be smoothly hydrolysed in a basic medium to give (*S*)-**19** in high yield as a sole product.

3.3 Imiprothrin a synthetic pyrethroid with high knockdown activity

3.3.1 Background

When we had prallethrin in hand, we next wanted a much stronger knockdown agent against cockroaches. We therefore re-designed the structure of the alcohol moiety of prallethrin by analogy to tetramethrin and by merging with the structure of hydantoin fungicides **25**, imiprothrin (**26**) was finally synthesised by Itaya[12] (Fig. 11).

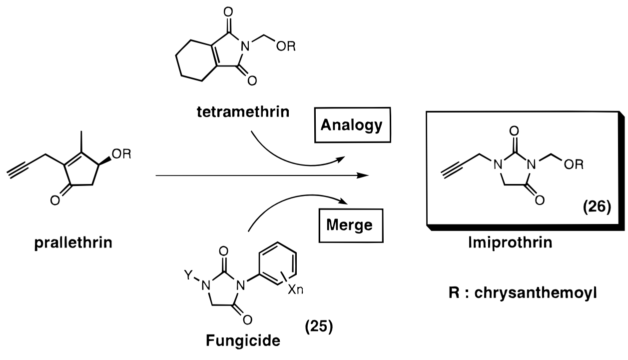

Fig. 11. Background of imiprothrin (Itaya 1979).

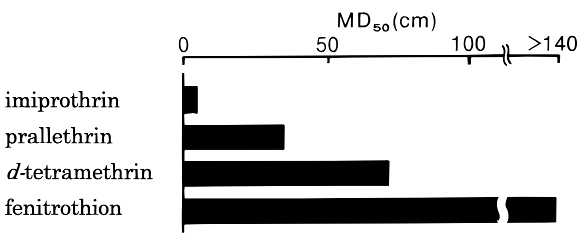

Fig. 12. Moving distance of german cockroaches after treatment with 1.0% oil-based aerosol formulation.

3.3.2 Knockdown activity of imiprothrin

Imiprothrin has great knockdown activity against cockroaches. Figure 12 shows the mean distances (MD_{50}) travelled by the cockroaches in the 'Darts' test (Section 2.1.1); that for imiprothrin (**26**) was only 10 cm compared with 35 cm for prallethrin and 70 cm for tetramethrin.

3.4 Stereochemical relationship of three synthetic pyrethroids

Stereochemical resemblance of the three synthetic pyrethroids empenthrin, prallethrin and imiprothrin was studied with computer modelling by Kurita. (Kurita, Y., unpublished) The closer analogue **16** of empenthrin was selected so that each alcohol had the same terminal propynyl group. As mentioned, (*S*)-empenthrin, or (*S*)-α-ethynyl-2-methylpent-2-enyl (1*R*)-*trans*-chrysanthemate is much more insecticidal than (*R*)-empenthrin, or (*R*)-α-

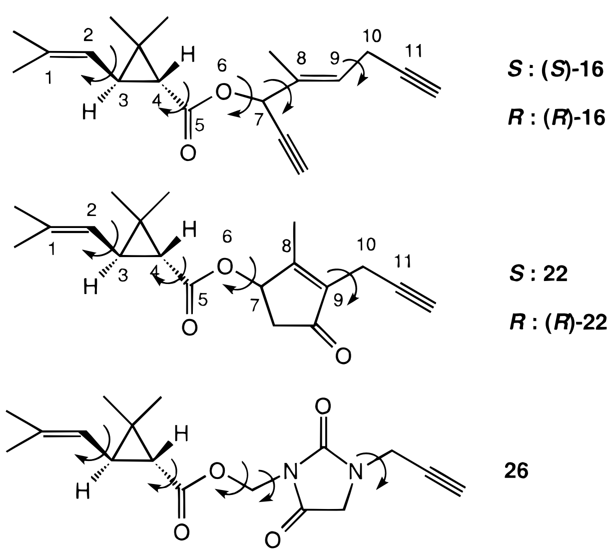

Fig. 13. Rotatable bonds of three synthetic pyrethroids (Kurita, 1996).

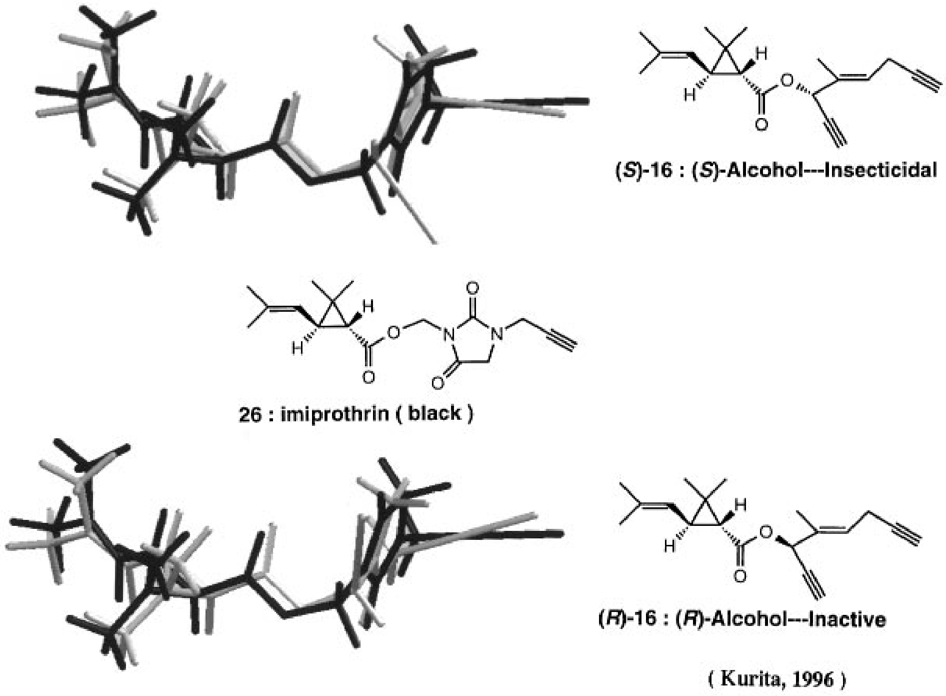

Fig. 14. Superposition of imiprothrin with (*S*)- and (*R*)-propargyl analogue of empenthrin.

ethynyl-2-methylpent-2-enyl (1*R*)-*trans*-chrysanthemate. That is the case in the propynyl analogue, **16**, of empenthrin.

With regard to prallethrin, (*S*)-2-methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl (1*R*)-*trans*-chrysanthemate is the most active isomer, and the ester of (*R*)-alcohol with (1*R*)-*trans*-chrysanthemic acid is only one eightieth as active as the (*S*)-alcohol ester. As the alcohol moiety of imiprothrin is achiral, it is easy to compare the most stable conformer of imiprothrin with the present four stereoisomers of two synthetic pyrethroids in order to obtain the stereochemical relationship of three synthetic pyrethroids.

In Fig. 13 are shown the structures of these three synthetic pyrethroids. Bonds with arrows are defined as rotatable. The (*S*)-propynyl analogue, (*S*)-**16**, and the (*R*)-propynyl analogue, (*R*)-**16**, of empenthrin superposed with imiprothrin (**26**) are shown in Fig. 14. At the

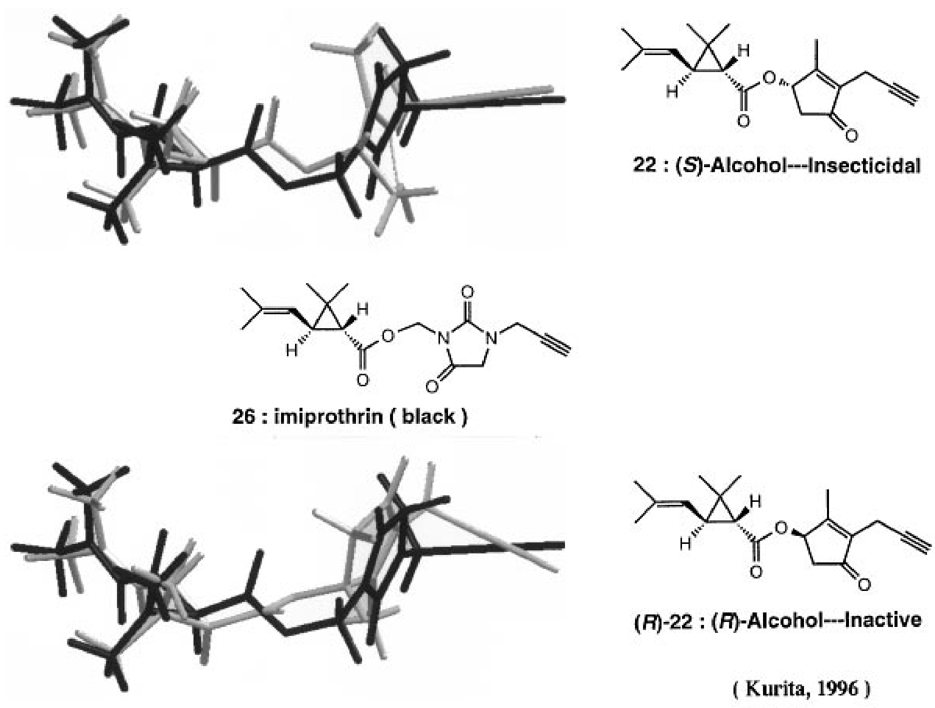

Fig. 15. Superposition of imiprothrin with prallethrin and its (*R*)-isomer.

top, the insecticidal (*S*)-**16**, coloured white, and imiprothrin, coloured black, overlap well. Insecticidally inactive (*R*)-**16**, coloured white, and imiprothrin are superposed at the bottom. The propynyl portion of (*R*)-**16** extends in a slightly different direction. Other portions overlap well with each other except the α-ethynyl moiety. However, the energy level of this (*R*)-**16** conformer as shown is about 2 kcal mol^{-1} higher than that of the (*S*)-**16** conformer shown, which means the probability of this most fitted conformer of (*R*)-**16** is relatively lower than that of (*S*)-**16**.

On the other hand, superimposition of (1*R*)-*trans*-prallethrin (coloured white) and imiprothrin (coloured black) is shown at the top in Fig. 15. They overlap well, whereas the insecticidally inactive (*R*)-isomer of prallethrin, (*R*)-**22** (coloured white) at the bottom could not be superposed well with regard to propynyl and ester functions. Thus, shape of the pyrethroid receptor site is not fully characterised. However, the present study will provide greater insight into the essential stereochemical requirements for synthetic pyrethroids.

4 SUMMARY AND CONCLUSION

A series of three different inventions is summarised in Fig. 16, which stemmed from an unexpected reaction during process research on furamethrin. Subsequently, process research with optically active α-ethynyl alcohols gave us a clue to the next discovery, prallethrin. In turn, prallethrin became a guide-post to the next invention and was transformed to imiprothrin by analogy and by

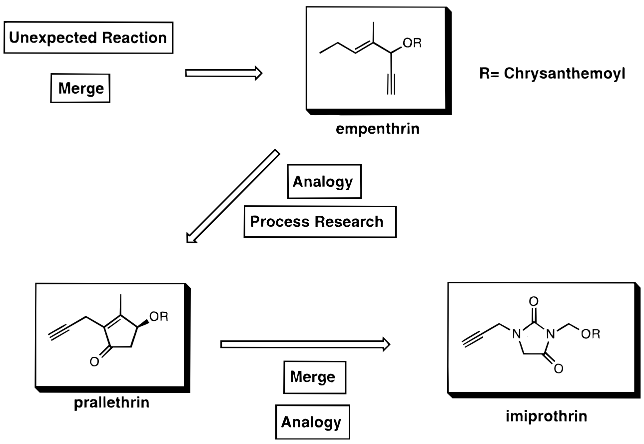

Fig. 16. Summary of inventive story.

merging other bioactive structures. Although the discovery of a new pesticide tends to be more and more difficult due to a lot of competitive compounds and higher barriers of safety evaluations, recently computer modelling and combinatorial chemistry have been making remarkable progress to aid the lead generation and lead evolution processes. However, I believe that a lucky and/or painstaking individual researcher following factors such as those mentioned can still make valuable new discoveries.

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